＜Research Note＞

Adverse Events of Prescription Drugs Approved "before" Clinical Tests Are Completed, and Defects in Product Liability Law(1)

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Keywords: Product Liability, Prescription Drug, Clinical Test,
Adverse Event, Defect

1. Introduction

I will examine the principles that underpin this field, and consider some international comparisons.

Imagine you have a serious illness and conventional drugs are not working. Your doctor suggests a new drug that might work. If you try this drug, and there is an adverse reaction, who pays the damages?

Industrialised countries typically have consumer protection laws that work well. But healthcare is a unique category. For example, if you tried a new anti-cancer drug and afterwards experienced an unexpected Adverse Drug Reaction, or "ADR", in some countries compensation would be small. This can be true even when there is proof of causation between the drug and the ADR.

The aim of this study is to consider, "what is the best form of a consumer protection in certain ADR cases".

In some jurisdictions, such as the EU, if the manufacturer of the drug that caused an ADR can prove there was no foreseeable defect in that product before delivery it can defend itself on "development risk" grounds.

But if the maker could not identify specific risks, how could the consumer?

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3. The Japanese Supreme Court Case
4. No-fault compensation schemes for ADR
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I focus on the product liability for prescription drugs that lead to ADRs.

For this study, I assume that intermediaries such as doctors act properly, and I therefore disregard 'the Learned Intermediary Doctrine' and issues of Informed Consent.

Also, the study does not cover compensation for clinical test participants, which is a separate case.

First, I discuss ADR risks and associated warnings under Japanese law.

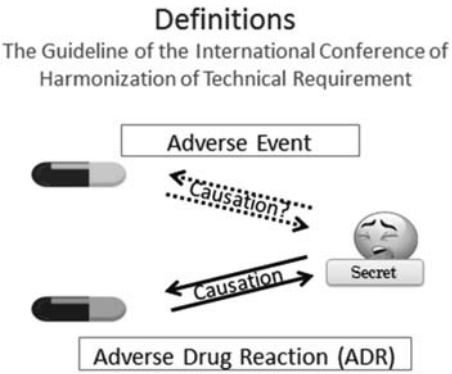
Second, I highlight a Japanese Supreme Court case in which a maker is absolved of responsibility for defective goods without using the "development risks" defence.

Third, I compare no-fault compensation schemes for prescription drugs.

Let me define some terms according to the ICH-E2A.[(2)]

An 'Adverse Event' is any untoward medical occurrence in a patient who has been administered a pharmaceutical product which does not necessarily have a direct causal relationship with the treatment.

An 'Adverse Drug Reaction', or 'ADR', refers to cases where a causal relationship between a medical product and an adverse event is at least a reasonable possibility.



2. ADR risks and associated warnings under Japanese Law

First, I will outline the Japanese Product Liability Act 1994.

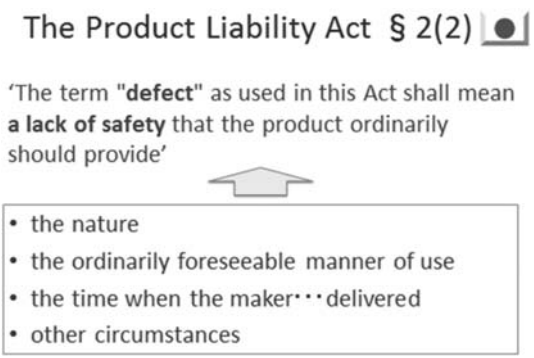
Section 3 states, 'The manufacturer … shall be liable for damages arising from the infringement of life, body or property of others which is caused by the defect in the delivered product which was manufactured, processed, imported, or provided with the representation of name …'

This act has important differences with consumer protection regimes in the UK and Germany.

For example, the Japanese act's Section two-point-two provides that 'The term "defect" as used in this Act shall mean a lack of safety that the product ordinarily should provide, taking into account the nature of the product, the ordinarily foreseeable manner of use of the product, … and other circumstances concerning the product.'

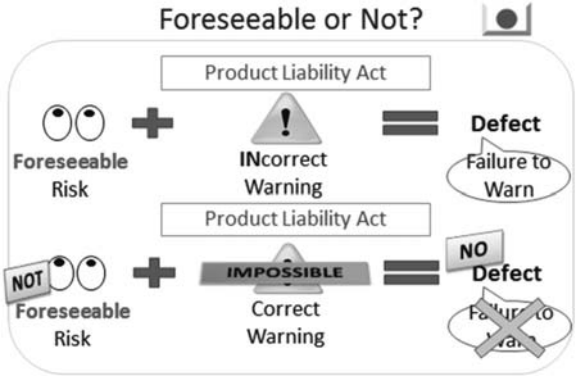
Importantly, Japanese legislators deliberately avoided using a consumer expectation criterion.

To be clear, in Japan, if the maker has foreseen or might foresee the drug's risk, and the maker did not warn about such risk, the drug shall be deemed



defective under the Product Liability Act.

I now discuss the risk of ADR and associated warnings under Japanese law. Arguably, drugs always have "unforeseen" risks.



During development and manufacture, if makers identify potential adverse events associated with the drugs they are legally obliged to warn users of the risks.

However, if experts could not identify any likely, specific adverse event associated with the drugs, the makers obviously could not issue warnings through package inserts.

Therefore, under Japanese law, a manufacturer can defend itself on the grounds that the adverse events were not foreseeable; this is similar to the "development risk defence" of other jurisdictions, but without using the same technical terms.

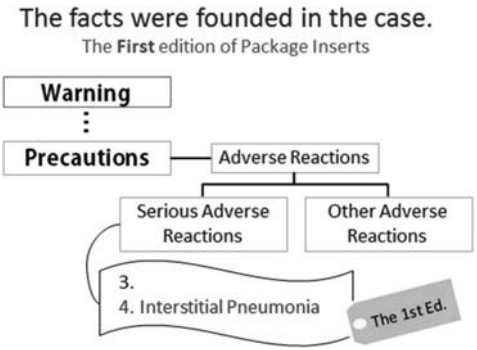
3. The Japanese Supreme Court Case[(3)]

I turn now to a particular Japan Supreme Court decision.
A difficulty in these cases is that the judge must decide what could reasonably be foreseen at the product launch time.
It's hard to prove for the maker that there is no causal relationship between a product defect and the damage. It's much easier to prove that there is no foreseeable ADR given the state of (scientific or technical) knowledge at drug delivery. Judges must decide what is foreseeable, and judges don't always interpret laws as the legislators had intended.

Almost 10 years ago, a new drug for non-small-cell lung cancer was approved and delivered to market before clinical test completion. Anti-cancer drugs are sometimes released before the third clinical test, as suitable test participants are hard to find.
The new anti-cancer drug was effective in shrinking tumours of particular participants.
In cases of interstitial pneumonia that were reported in clinical trials in Japan, the US, and the UK, there were only weak suspicions about a causal relationship between the administration of this drug and harmful effects.

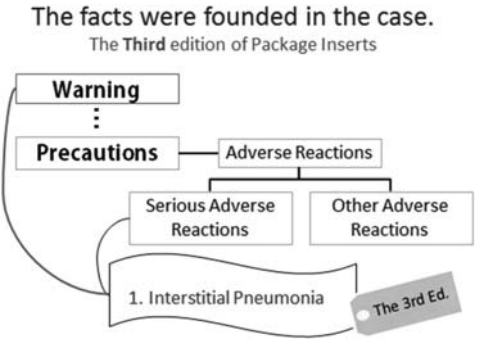
The UK-based maker of the drug obtained official approval to import into Japan.

It then produced 'warning' and 'precaution for use' package inserts. The package insert Warning should be used when there is a possibility of severe adverse reactions and so special attention is called for.



"The 'Precautions for Use' section, designed to provide doctors with necessary information, must have an 'Adverse reactions' section, with 'Serious Adverse reactions' and 'Other Adverse reactions' sections.

Effects of the drug that need special attention should be described as 'Serious Adverse reactions'.



In this case, pneumonia had been listed not in the 'Warning' section, but was listed as the fourth of the 'Serious Adverse reactions'.

Three months after the product's Japan launch, 34 pneumonia cases were

reported; seventeen of them fatal.

In the third edition of the package insert, pneumonia was added to the 'Warning' and listed top in 'Serious Adverse reactions'.
Patients filed a complaint against the maker, arguing that the information on pneumonia as a potentially fatal adverse reaction of the drug should have been provided when import approval was granted.

However, the Japanese Supreme Court ruled as follows:

> "Drugs, due to the nature of being foreign to the human body, are considered to cause some hazardous adverse reactions unavoidably, and the mere existence of adverse reactions of a drug therefore cannot immediately be regarded as meaning that the drug is a defective product. Rather, the safety that a drug ordinarily should provide can be secured by appropriately providing necessary information for using the drug as a product with regard to the drug's adverse reactions that are foreseeable at the time of its delivery from its ordinarily expected manner of use, and in light of such relation, there may be cases in which the failure to provide such information on adverse reactions appropriately could be a reason for finding a defect in the drug."
>
> "According to the facts mentioned above, in the case of an ethical drug, such information on adverse reactions should be described appropriately in its package insert, and it is reasonable to construe that whether or not the description in the package insert is appropriate should be judged by taking into consideration various factors concerned, including the details and degree of the adverse reactions (including the frequency of occurrence), the knowledge and skill that the prescriber or user are ordinarily expected to have in light of the effect of the drug, and the format or style by which the adverse reactions are described in

the package insert, and then examining whether or not the risk of such foreseeable adverse reactions is sufficiently disclosed to the prescriber or user."

The court ruled that the description in the first edition of the package insert had not become inappropriate as a description of foreseeable adverse reactions during the period after import approval was granted and before drug administration began. Thus the complainants lost.

4. No-fault compensation schemes for ADR

I look now at "No-fault Compensation systems" for pharmaceuticals.[(4)]

Some countries, including Japan, France and Finland, have "no-fault" compensation schemes for ADR.

Japan's 'Relief System for ADR' provides relief benefits for health damage from drugs such as effects requiring hospitalization.

Japan's compensation system has two main characteristics.

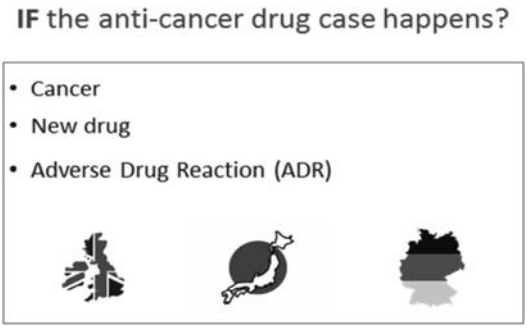
One is its exemptions - for example, for anti-cancer drugs - which are more numerous than the German systems.

Thus, a terminally ill patient can be administered mixed treatments, and the drug and doctor cannot easily be sued if things go wrong.

The second main characteristic is that a causal link between ADR and consequent damage to health is necessary if compensation is to be paid. This requirement limits compensation pay-outs.(5)

5. International comparisons

Let's return to the anti-cancer drug case.



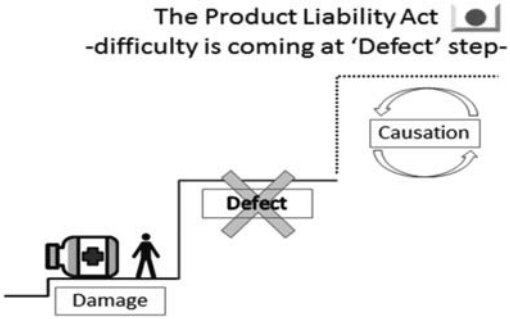
The consumer had cancer, took a new drug, and suffered an ADR caused by the drug.

The danger of "some" ADR was known, but obviously it hadn't been anticipated that treatment would lead to fatalities.

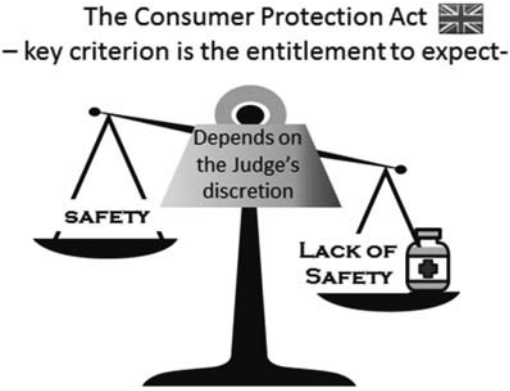
In such cases in Japan, the UK and Germany, how would consumers get the damages or compensation?

In the Japanese case, the court ruled that there was no failure to warn, as the description about the adverse reaction at the time of delivery was appropriate given the state of knowledge at that time.

And, the consumers could not get compensation under the Japanese "no-fault" compensation scheme for ADR, as the anti-cancer drug is excluded from its application.



Next, I consider the UK's Consumer Protection Act 1987.



In the UK, the ADR caused by the anti-cancer drug might be regarded as a defect, because of a lack of safety that 'the public was entitled to expect'.

In Worsley v Tambrands Ltd,(6) a consumer got toxic shock syndrome, "T. S. S.", through using a tampon. Though a direct warning about the dangers was printed on the packaging, and consumers were advised to "Read and save the enclosed leaflet", the consumer threw her leaflet away.

The Judge said;

> '... the duty of the manufacturer and that to which persons generally are entitled to expect in relation to the product, is that the box contains

an unambiguous … warning that there is an association between T. S. S. and tampon use and directs the (user)… to the internal leaflet for full details.

TSS is a rare but potentially very serious condition which may be life threatening, but it is necessary to balance the rarity and the gravity. That balance is reasonably … struck by the dual system of a risk warning on the box and a full explanation in the leaflet …'

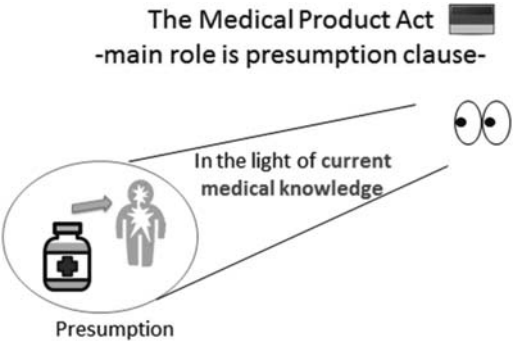
The anti-cancer drug case and the Worsley case both had product warnings. However, the risk level of the tampon was clear, but the anti-cancer drug's was unclear.

Yet in both cases the judges found the warnings sufficient.

Also, in the UK, even if the Judge were to recognize the "development risk" defence by the maker, the consumer can obtain free healthcare from the N. H. S. for the effects of the ADR.

As shown in table 2 I distributed, although the UK does not have any "no-fault" compensation schemes for medicinal drug-related injuries, compensation is available in some cases, like vaccine-related damage. Also, as noted, there is free care from the N. H. S.

Thus the UK's support is much more extensive than support in Japan.



In Germany, there is a presumption clause in the Medical Product Act 1976. If a consumer were substantially damaged as a result of the administration of the drug, the maker is obliged to pay compensation.

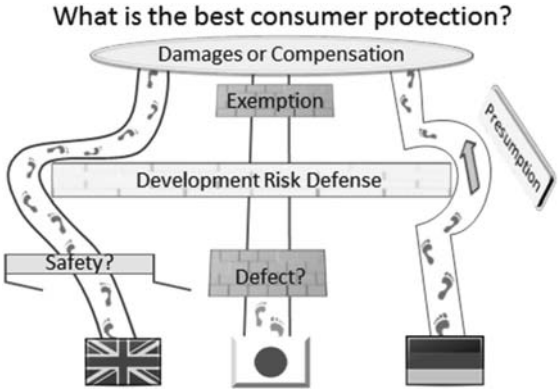
To avoid that liability, the maker would have to prove that the adverse event is not due to its development and manufacturing process.

There is a notable difference compared with Japanese and UK laws; namely, Japanese and UK laws focus on whether the "ADR" could reasonably be anticipated by the maker under the state of knowledge at the time of delivery.

Germany's Medical Product Act is a "one-stop law": The consumer deemed to have suffered the ADR could be compensated under a combination of civil law, civil procedure, and administrative law schemes. Access to compensation is thus easier than under the Japanese system.

6. Conclusion

In conclusion, in cases where a prescription drug causes an ADR, Japan's product liability law is the least consumer friendly.



Critically, unlike in the UK, Japanese legislators did not write a "consumer standard" criterion into the provisions.

Also, the Japanese no-fault compensation scheme for ADR is weaker than that of the UK; although the UK has no specific "no-fault" compensation scheme, the consumer might win damages under the Consumer Protection Act, which provides a high level of consumer protection, including for prescription drugs. The German system is different again. There, different types of laws coexist. One law applies for general defective goods; another applies only in medically significant injury cases.

Thus, a German consumer who suffered an ADR might get compensation using the one-stop scheme. In contrast, although the UK has no comprehensive no-fault compensation scheme for ADR, the Consumer Protection Act applies for all kinds of goods and those who suffered an ADR might get damages under that Act.

Japan's legislature examined other countries' laws while drafting the Product Liability Act and no-fault compensation scheme, and it then established one product liability law applicable to almost all goods.

However, the exemptions created were disadvantageous for consumers.

The Japanese legislators should re-examine the law covering compensation for ADRs in the light of other countries' legal regimes, in order to provide Japanese consumers with the best possible consumer protection law.

〔Notes〕

(1) This research note was a handout which I had presented at a workshop of the 15th International Association of Consumer Law Conference hosted by University of Amsterdam, 1st July 2015.

(2) 'Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A' of 'The Guidelines of the International Conference on Harmonisation of Technical Requirements for the registration of pharmaceuticals for human use', http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf.

(3) Judgement of the Third Petty Bench of the Japanese Supreme Court 12.4.

2013, Case No. 2012（Ju）293, Minshu Vol. 67 No. 4 pp. 899. You can read full text of the decision; http://www.courts.go.jp/app/hanrei_en/detail?id＝1193.

（4） Please refer to the Table 2 in Appendix.

（5） The study group of considering the compensation scheme for adverse event suffered from anti-cancer drug, 'The outline of compensation schemes for ADR in foreign countries', The 5th Appendix at the 8th meeting (25.4.2012), digital copy in Japanese is as follows; http://www.mhlw.go.jp/stf/shingi/2r98520000029bo7-att/2r98520000029btq.pdf, 'The Result of Considering about the Compensation scheme for adverse event suffered from the anti-cancer drug', 10.8.2012, digital copy in Japanese is as follows; https://nk.jiho.jp/servlet/nk/release/pdf/1226566361730, Hideki MAEDA and Tatsuo KUROKAWA, Involvement of Anticancer Drugs in the Relief System for Adverse Drug Reaction in Japan', JJCO 2013;43:812:91273-1281, 25.9.2013, the digital copy in English is as follows; http://jjco.oxfordjournals.org/content/43/12/1273.long. All links are checked on 05/06/2015.

（6） Worsley v Tambrands Ltd. [1999] EWHC 273 (QB) (03 December 1999)